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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/902,572	07/10/2001	Avi Ashkenazi	GNE.1618P2C40	5445

9157 7590 03/16/2004

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EXAMINER	
LEFFERS JR, GERALD G	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 03/16/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/902,572	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Gerald G Leffers Jr., PhD	1636	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 02 March 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 6 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.
ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☒ The proposed amendment(s) will not be entered because:

   (a) ☒ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☒ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: *please see the attachment*.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *please see the attached sheets*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☒ will not be entered or b)☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *39-43*.

   Claim(s) withdrawn from consideration: _____.

8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☐ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). _____.

10. ☐ Other: _____

Gerald G Leffers Jr., PhD
Primary Examiner
Art Unit: 1636

ADVISORY ACTION ATTACHMENT

2. Non-Entry of the Amendment

The proposed amendment has not been entered as it changes the scope of the claims and necessitates a new prior art search (i.e. an "isolated" antibody).

5. Request for Reconsideration

Arguments directed to the amended claims are moot, as the amendment has not been entered. Many of applicants' arguments are a repeat of arguments previously presented. In response, the examiner's comments and grounds of rejection are incorporated here by reference.

Response to Arguments/Utility

With regard to the rejection made under 35 U.S.C. 101 for lack of a substantial and specific utility, the response essentially argues: **1)** Exhibits A and B demonstrate how effective PRO302 is at inducing vascular permeability and show that it is easy to monitor the ability of polypeptides like PRO302 to induce vascular leakage compared to a negative and positive control, **2)** based on these results, the skilled artisan would know how to use anti-PRO302 antagonists (e.g. antibodies) to stop vascular leakage associated with different conditions (e.g. pulmonary leakage, capillary leakage, tumor leakage or in burns), **3)** such uses are substantial and specific and would be clearly evident to the skilled artisan, **4)** the MPEP 2107.01 states that the examiner should not interpret the phrase "immediate benefit to the public" or similar formulations to mean that an invention must be currently available to the public in order to satisfy the utility requirement, and that any reasonable use that an applicant has identified for the

invention that can be viewed as providing a public benefit should be accepted as sufficient to describe a "substantial" utility, and **5)** if the applicant has asserted that the claimed invention is useful for any particular practical purpose, and the assertion would be considered credible by a person of ordinary skill in the art, the utility rejection should not be made.

At no point has the examiner cast the rejection in terms of a lack of credible utility. Rather, the rejection has been made in terms of a lack of a specific and substantial utility that does not require further experimentation to identify a real world use for the claimed invention. This does not, as the response implies, mean the examiner is applying a standard that the invention must be "readily available" to the public. There is no requirement that the invention be "readily available" to the public (e.g. already reduced to practice). Again, the grounds of rejection are directed to a lack of a specific, substantial utility that does not require further experimentation for confirmation of such utility.

For example, even though applicants' exhibits and specification clearly demonstrate that injection of the PRO302 protein intra-dermally in guinea pigs will cause some vascular leakage, there is no convincing evidence or rational that PRO302 plays any role whatsoever in vascular leakage in its usual role(s) *in vivo* (e.g. mediating vascular permeability in response to any particular condition or event such as burns or tumor growth). In other words, there is no convincing evidence or argument for a specific role for PRO302 in any process or condition that involves vascular integrity (e.g. pulmonary leakage, capillary leakage, tumor leakage or in burns). The fact is that applicants have only demonstrated that injection of large quantities of this protein can cause some vascular leakage in lab rodents. The skilled artisan would still have had to confirm that PRO302 plays some role in vascular physiology as part of its normal

functions in the body in order to demonstrate a substantial utility for the protein in identifying antagonists of this particular activity. One cannot consider that developing antagonists to a protein that may only be involved in disrupting vascular integrity upon injection in large quantities under the skin, a completely artificial situation, as a "real world" application in and of itself.

With regard to applicants' data presented in Exhibits A & B, it is clear that PRO302 does invoke at least some vascular leakage when injected intra-dermally in guinea pigs. It is noted, however, that the degree of induced permeabilization is substantially less for PRO302 as compared to the positive control, even when ten times as much (by weight) PRO302 protein is injected. It is conceded that the examiner has not done the calculations to determine the molar ration of PRO302/VEGF used in the experiments, nor taken into account any differences in activity that might be due to how the different proteins were prepared, but the data as presented in the Exhibits do not appear be so impressive as to suggest that PRO302 normally has a role in vascular permeabilization.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr., PhD whose telephone number is (571) 272-0772. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gerald G Leffers Jr., PhD
Primary Examiner
Art Unit 1636

GERRY LEFFERS
PRIMARY EXAMINER